Stress echocardiography beyond coronary artery disease

E. Schwammenthal, Z. Vered, B. Rabinowitz, E. Kaplinsky and M. S. Feinberg

Heart Institute, Chaim Sheba Medical Center, Tel Hashomer and Sackler School of Medicine, Tel Aviv University, Israel

Doppler echocardiography has become the major diagnostic tool of evaluation of valvular heart disease and the cardiomyopathies because of its ability to provide valuable haemodynamic information accurately and non-invasively. It is therefore ideally suited for haemodynamic stress testing in these patients.

In aortic stenosis, dobutamine echocardiography can distinguish severe from non-severe stenosis in patients with depressed left ventricular function, low transvalvular gradients, and a relatively small (flow-related) valve area at baseline. Patients with non-severe aortic stenosis increase cardiac output and valve area with dobutamine infusion while the transvalvular gradient does not change significantly. In severe aortic stenosis, the pressure gradient increases significantly with stroke volume, but valve area does not. In patients who fail to increase stroke volume (absent contractile reserve) and therefore do not show a change in haemodynamics, the severity of the lesion is 'indeterminate'; these patients are characterized by a very poor prognosis.

In mitral stenosis, patients can be identified who increase valve area during exercise, which is the fundamental mechanism by which stroke volume can be increased in mitral stenosis. The increase in pulmonary artery pressure during exercise (assessed from tricuspid regurgitant signal) can be dramatically different in patients with comparable resting haemodynamics; therefore exercise echocardiography provides information which cannot be obtained from resting measurements alone and can help to guide medical and surgical therapy.

Whether stress echocardiography may be similarly helpful in patients with regurgitant lesions is still a subject of investigation. Exercise Doppler echocardiographic studies following aortic valve replacement (small valves) can identify impairment of systolic and diastolic function indicative of 'valve prosthesis–patient mismatch'. In hypertrophic cardiomyopathy the dynamics of outflow obstruction can be assessed following exercise or pharmacological intervention. In dilative cardiomyopathy, contractile reserve can be assessed by dobutamine echocardiography which may help in evaluating prognosis, guiding heart failure therapy, and monitoring therapy with cardiotoxic chemotherapeutic agents.

Introduction

Doppler echocardiography has become the major diagnostic tool for assessment of valvular heart disease and the various forms of cardiomyopathy because of its ability to provide valuable haemodynamic information accurately and non-invasively. It would therefore seem ideally suited for application in stress testing and objective assessment of exercise physiology in these patients. However, in contrast to the widespread use of stress echocardiography in ischaemic heart disease, its use in valvular and myocardial diseases has been limited. The present review will detail some important haemodynamic aspects in valvular and myocardial diseases which have been elucidated by stress echocardiography, focusing primarily on what in the authors' opinion can be regarded as established indications for stress echocardiography in 'non-coronary artery disease'.
left ventricular function is usually straightforward, patients with significantly impaired left ventricular function and relatively low gradients pose a serious diagnostic challenge: Is the low gradient the consequence of low cardiac output across a severely stenotic valve which has led to severe depression of left ventricular function or is the low gradient an expression of coincidental non-significant aortic valve disease in severe left ventricular dysfunction unrelated to aortic stenosis?

Finding the right answer to this question is of immense clinical importance. In the first case, aortic valve replacement would be warranted which has been shown to dramatically improve and in most cases even normalize left ventricular performance by removing the excessive afterload burden; substantial improvement even occurs in patients with long-standing disease and ejection fraction below 20%\(^5\). In the second case aortic valve replacement will not cause any beneficial effect and only endanger the patient's life (it would essentially come close to replacing a mildly stenotic aortic valve in severe dilative cardiomyopathy).

For some time, assessment of aortic valve area has been considered the answer to this question, because it has been assumed that while the pressure gradient is flow dependent, stenotic valve area is fixed, producing high pressure gradients at normal and low pressure gradients at low cardiac output. However, it has been shown that valve areas calculated by the Gorlin formula usually increase with flow\(^8\).\(^9\). It has been argued that this increase might merely represent the flow-dependence of the empirical constant C (discharge coefficient) of the Gorlin formula, which represents the ratio of effective to anatomical orifice area\(^6\). Based on studies in bioprostheses with known orifice size it has been argued that the discharge coefficient may be smaller at lower flow rates and that assuming a constant (high) discharge coefficient therefore results in ‘under-estimation’ of the true anatomical valve area by the Gorlin formula at low flow rates\(^8\).\(^9\). However, these experiments had been performed in bioprosthesis which might actually stretch with flow, as has been reported\(^10\),\(^11\), so that actual changes of anatomical valve area might have been interpreted as changes in the discharge coefficient.

Moreover, in vitro studies of truly fixed (rigid) orifice geometries have suggested that the discharge coefficient is constant with physiological limits\(^11\)-\(^13\). Burwash et al., who studied 66 asymptomatic patients with aortic stenosis, therefore interpreted an increase in effective aortic valve area (by continuity equation) during stress-echocardiography as a flow-dependent increase in actual orifice area\(^14\). Because of this flow-dependence, however, assessment of valve area, does not solve the diagnostic dilemma in patients with aortic stenosis, low gradients and depressed left ventricular function. This has been most clearly highlighted by Cannon et al. who showed that some patients with left ventricular dysfunction and low gradients have calculated valve areas indicating critical aortic stenosis when the valve does not seem significantly diseased at all at surgery\(^15\). It has therefore become practice in many catheterization laboratories to perform manoeuvres (e.g. nitroprusside infusion) to increase cardiac output, so that valve area can be calculated at a higher flow rate.

It would be desirable to distinguish between severe fixed and flow-dependent (relative) aortic stenosis in patients with left ventricular dysfunction, low gradients, and low valve areas (at baseline) before they end up in the catheterization laboratory. That this is possible has been demonstrated by deFilippi et al. who studied 18 such patients, ranging in age from 56 to 88 years, by dobutamine echocardiography (up to 20 \(\mu\)g·kg\(^{-1}\)·min\(^{-1}\))\(^16\). Eight patients (44%) had significant coronary artery disease. Ejection fraction ranged from 20% to 38%, mean gradients from 17 to 30 mmHg, peak gradients from 21 to 58 mmHg, and aortic valve area from 0.6 to 0.9 cm\(^2\).

The study demonstrated that dobutamine echocardiography can discriminate three distinct haemodynamic subsets: (1) patients with preserved contractile reserve (\(\geq 20\%\) increase in wall motion score) who show a valve area increase of \(\geq 0.3\) cm\(^2\) without a substantial increase in gradient with dobutamine infusion — these patients are considered to have left ventricular dysfunction unrelated to (relatively mild) aortic valve disease and should be treated conservatively. (2) Patients with preserved left ventricular contractile reserve who show no significant increase in valve area, but an increase in pressure gradient — these patients have severe (fixed) aortic valve disease and should undergo surgery, which they did in the quoted study; surgery revealed severe calcific aortic valve stenosis in all of them, and relieved symptoms and improved left ventricular function in three of the four patients (one died peri-operatively). (3) Patients without contractile reserve — in these patients the severity of aortic stenosis cannot be determined unambiguously because they are unable to increase their cardiac output with dobutamine. In the quoted study, this group had a very poor prognosis; within 1 year three of six patients died (including the one who underwent balloon valvuloplasty), the other three developed congestive heart failure.

Although a large prospective study is definitely warranted, based on growing echocardiographic experience, as well as experience with pharmacological intervention in the catheterization laboratory, we consider dobutamine echocardiography to be a safe and reliable technique to distinguish between severe (fixed) and relatively mild aortic stenosis in the presence of low gradients and poor left ventricular function. The following points, however, should be considered when interpreting the results of a dobutamine study in these patients:

(1) An increase in anatomical valve area caused by an increase in flow can occur both in mild and severe aortic stenosis\(^14\). Therefore, we do not think that an increase in valve area by \(0.3\) cm\(^2\) (e.g. from 0.5-0.6 to 0.8-0.9 cm\(^2\)) can definitively rule out significant aortic stenosis. In contrast to deFilippi et al., we therefore use an absolute cut-off value at peak dobutamine (>1.0 cm\(^2\)) as...
an additional major criterion required to rule out severe aortic valve stenosis, rather than an increase of ≥0.3 cm² from baseline alone. This is also in keeping with the protocol used by the group of Carabello for pharmacological intervention in the catheterization laboratory.

(2) So far, we have not encountered patients with a valve area of (significantly) less than 0.6 cm² at baseline, who did not have severe aortic stenosis. Usually these patients have mean gradients of more than 30 mmHg, and frequently more than 50 mmHg. Whether dobutamine echocardiography is helpful in this patient group is unclear at this stage.

(3) Patients who fail to increase wall motion score or systolic flow significantly ('indeterminate' severity of aortic stenosis) have been shown to represent a group with a very poor prognosis. The therapeutic implications of this are unclear.

**Mitral stenosis**

There are several reasons why assessment of exercise haemodynamics is desirable in mitral stenosis: symptoms are only roughly correlated to measurements of valve area at rest. They develop insidiously over years with patients adapting their lifestyle to those limitations to an extent that they no longer perceive them as abnormal (frequently being aware of them only after valve replacement). Although functional class is strongly associated with survival (5-year survival rate decreases from more than 90% in class I, to roughly 60% in class II, less than 50% in class III, to 0% in class IV) [17,18], distinction between functional classes II and III is most problematic, and influenced by peripheral adaptation [19], training and co-morbidity. While the capability of performing 10 min of exercise on a standard treadmill protocol clearly rules out severe disease, probably obviating the need for Doppler echocardiographic assessment of exercise haemodynamics, a low exercise capability e.g. in an overweight, untrained patient with mitral stenosis, does not automatically imply severe valve disease as the cause of limitation. On the other hand, the finding of a significant increase in pulmonary artery pressure during low-level exercise in an asymptomatic female with moderate mitral stenosis who wishes to become pregnant may be of great therapeutic implication.

Voelker et al. demonstrated in a simultaneous Doppler–catheterization study that the increase in mean transmirtal pressure gradients at exercise between both methods is highly correlated (r=0.90) with a standard error of estimate of less than 2 mmHg [20]. The same group reported a variable response of mitral valve area to an exercise-induced increase in flow, with a distinct group of patients being able to increase valve area substantially during exercise. The authors concluded that such changes have to be taken into account when evaluating the functional significance of the obstruction. Dahan et al. demonstrated that the fundamental mechanism by which patients with mitral stenosis can increase their stroke volume during exercise (despite shortening of the diastolic filling period with tachycardia) is an increase in mitral valve area [21], and the major determinant for the ability of the mitral valve to increase in area during exercise is the severity of pathoanatomical changes as assessed by the mitral valve score. In a preliminary series of 20 patients, we came to similar results, and found that while an increase in valve area can significantly increase stroke volume, even doubling the pressure gradient will not effectively increase stroke volume in significant mitral stenosis, which is in accordance with the square root relationship between transvalvular flow and pressure gradient embedded in the Bernoulli equation.

It is imperative that assessment of mitral valve area at rest and during exercise be performed by the continuity equation and not the pressure half-time method, since the latter is dependent on atriioventricular compliance, which decreases during exercise, thereby shortening pressure-half time even when valve area actually remains unchanged [22]. Disregarding this fundamental limitation of the pressure half-time method has led to the erroneous perception of a substantial increase in mechanical prosthetic valve area during exercise in the study by Leavitt et al. [23]. Although a mild increase in effective mechanical prosthetic valve area has been reported [24], detailed in vitro studies have shown that effective orifice area of mechanical prostheses are fairly constant for physiological flow rates [25]. In the absence of significant aortic or mitral regurgitation, valve area can be calculated as aortic stroke volume divided by mitral time velocity integral. In contrast to Dahan et al. we use pulsed wave Doppler echocardiography in the left ventricular outflow tract and not continuous wave Doppler to determine aortic stroke volume, since this method is probably more accurate and avoids overestimation [26].

The Achilles' heel of echocardiographic stroke volume calculation is probably the measurement of left ventricular outflow tract diameter, a measurement which is squared to obtain valve area, potentiating any measurement error. Since it has been demonstrated both in normal subjects [27] as well in patients with mitral stenosis [28] that aortic stroke volume increases by an increase in aortic time-velocity integral while the size of the outflow tract remains constant, we use the same outflow tract area (determined at rest) for calculation of stroke volume during exercise, thereby eliminating the effect of measurement errors of the outflow tract dimension on the assessment of changes in stroke volume or valve area during exercise. In the presence of aortic regurgitation, pulmonary flow can be substituted for aortic flow; in the presence of mitral regurgitation (total) stroke volume can be calculated from end-diastolic and end-systolic volumes by two-dimensional echocardiography. Since calculations of stroke volume and valve area require non-simultaneous measurements at the aortic and mitral level, (supine) bicycle ergometry, rather than a treadmill study, should be performed for...
clinical decision-making was affected by the test results 41% and to treat medically in 52%. Our own data show data collection at comparable heart rates. In atrial in 85% including decisions to proceed to surgery in being considered. clinically established tool for assessing the functional correlated to the achieved increased in valve area 331; significantly shorter exercise capacity 301. Furthermore, pulmonary artery pressure during stress echocardiography found that patients with mitral stenosis who are limited by dyspnoea show a significantly greater increase in pulmonary artery pressure during stress echocardiography than those who are limited by fatigue, as well as as significantly shorter exercise capacity 300. Furthermore, clinical decision-making was affected by the test results in 85% including decisions to proceed to surgery in 41% and to treat medically in 52%. Our own data show that the increase in pulmonary artery pressure can be dramatically different in patients with comparable resting values of mitral valve area and pulmonary artery pressure, demonstrating that exercise-echocardiography provides haemodynamic information which cannot be obtained from resting measurements alone. Pulmonary artery pressure and its increase seem particularly high in patients with low atrioventricular compliance (which can be calculated non-invasively from the E-wave downslope and mitral orifice area), a group clinically characterized by dyspnoea at low level exercise, and a relatively short pressure half-time, which stands in contrast to a sizeable transvalvular pressure gradient and a significant reduction in mitral valve area by the continuity equation.

In some patients only faint tricuspid regurgitant velocity signals can be obtained, unsuitable for estimation of systolic pulmonary artery pressure. In these cases, enhancement of the signal by saline injection has been shown to provide good-quality tracings 301,321. However, such an approach requires the use of an echocardiographic machine with automatic gain control to prevent excessive noise (poor signal to noise ratio), unless newer albumin-based contrast agents are used.

Exercise Doppler echocardiography is ideally suited for the assessment of interventions such as percutaneous balloon commissurotomy. Tami et al. demonstrated a decrease in mean transmural pressure gradient at rest and during exercise, which was significantly correlated to the achieved increase in valve area 331; in addition heart rate during peak exercise decreased, suggesting a reduced need for compensatory tachycardia to augment cardiac output.

Based on these data, we believe that exercise Doppler echocardiography should be regarded as a clinically established tool for assessing the functional significance of mitral stenosis, particularly when discrepancies exist between the clinical picture and resting mitral valve area, or when procedural interventions are being considered.

Aortic regurgitation

The relationship between pre-operative left ventricular function and postoperative long-term survival is well established in aortic regurgitation 34-351,361. Similarly, symptomatic patients with aortic regurgitation and left ventricular dysfunction but preserved exercise capacity (>22-5 min) have a greater likelihood of postoperative reduction and normalization of left ventricular dilatation than patients with poor exercise capacity (≤22-5 min) 361. In contrast to these findings, the clinical value of detecting systolic dysfunction during exercise in patients with normal resting function is still unclear. Percy et al. studied 10 asymptomatic patients with aortic regurgitation and normal left ventricular function at rest, three of whom had decompensation of left ventricular function at a mean follow-up of 3-6 years 371. The authors found that fractional shortening after exercise and left ventricular wall stress both at rest and after exercise were significantly different in the patients who subsequently experienced clinical decompensation.

Increases in regurgitant jet area, which have been observed during sustained handgrip exercise 381 have to be interpreted with caution, because of the dependence of jet area on driving pressure (a moderate increase in aortic pressure may cause a small increase in regurgitant flow but a sizeable increase in jet area).

Currently, stress echocardiography, although promising, cannot be regarded as an established diagnostic tool for evaluating patients with aortic regurgitation.

Mitral regurgitation

The impact of the mitral regurgitation orifice on left ventricular afterload is complex. While afterload is decreased in acute mitral regurgitation, and increased in chronic aortic regurgitation, it is normal in compensated chronic mitral regurgitation (increasing with decompensation because the increase in systolic chamber dimensions increases wall stress) 391. Although a normal left ventricular pump function does therefore not necessary require muscle dysfunction in severe chronic mitral regurgitation, dysfunction at rest may occur at a later stage, and exercise echocardiography could potentially reveal latent dysfunction during exercise, assisting in optimal timing for surgery.

Exercise-echocardiographic studies have demonstrated that patients undergoing mitral valve repair had significantly higher postoperative resting and exercise ejection fraction than patients undergoing mitral valve replacement (resting: 55 ± 12% vs 40 ± 17%; exercise: 63 ± 11% vs 42 ± 17%) 401. Left ventricular shape at peak exercise, an important feature which can be quantitatively assessed by echocardiography (eccentricity index), became progressively more spherical in patients who underwent valve replacement than in those who underwent repair 401. Since left ventricular sphericity is an indicator of wall stress, dysfunction, and a poor prognosis in cardiomyopathy, it might have comparable implications in mitral valve disease.
As in mitral stenosis, systolic pulmonary artery pressure at peak exercise can be assessed, and Schiller et al. have used an abnormal increase as a means of timing surgery in more than 30 cases\textsuperscript{41}, although a controlled study has not been performed to date. Stress echocardiographic assessment of left ventricular function and pulmonary artery pressure is a promising tool for evaluating patients with mitral regurgitation before and after surgical intervention. However, controlled studies are necessary to establish its exact clinical value.

Recently, the development of severe dynamic regurgitation during upright bicycle ergometry has been reported in patients with mild mitral stenosis and regurgitation at rest\textsuperscript{42}. Although the observation is interesting, studies based on colour jet area can be critically affected by the change in driving pressure, particularly in the setting of mitral regurgitation, and an increase in jet area might simply reflect an increase in driving pressure, without a change or even a decrease in regurgitant flow rate. In a study by Heinle et al.\textsuperscript{11}, dobutamine infusion caused a decrease in the degree of mitral regurgitation in 61\% of patients with an ejection fraction <50\% and in 25\% of patients with an ejection fraction $\geq$ 50\%\textsuperscript{43}. New or worsening mitral regurgitation rarely developed and were not associated with an ischaemic response\textsuperscript{43}. It is conceivable that the decrease in left ventricular and mitral annular size and function caused by dobutamine is different from a response which would be observed after treadmill exercise. Keren et al. studied a group of patients with severe heart failure and mitral regurgitation during isometric exercise using quantitative Doppler echocardiography\textsuperscript{44}. They observed a fall in forward stroke volume associated with an increase in mitral regurgitant volume during isometric exercise, which increases systemic resistance and thereby afterload. In contrast, dobutamine (and nitroglycerine) infusion decreased mitral regurgitant volume and increased forward stroke volume both at rest and during isometric exercise\textsuperscript{45}. These studies support the concept that aggravation of mitral regurgitation contributes to reduced forward output in patients with severe congestive heart failure and that assessing the response of mitral regurgitation to medical therapy may be important in these patients.

**Prosthetic valves**

Evaluation of prosthetic valves by stress echocardiography has primarily focused on haemodynamic differences between valve types. Jaffe et al., studying matched patient groups after aortic valve replacement, found that allograft prostheses had significantly lower rest and exercise transprosthetic gradients\textsuperscript{46}. Other studies aimed at a comparison between different types of mechanical prostheses\textsuperscript{47,48}. A major limitation of such in vivo continuous wave Doppler comparisons of pressure gradients is that because of pronounced pressure recovery observed in bi-leaflet valve prostheses\textsuperscript{49} effective (recovered) transprosthetic gradients are overestimated. Elaborative in vitro testing (and catheter measurements) have demonstrated that bi-leaflet prostheses have a favourable performance profile particularly the St. Jude-type, compared with other mechanical and even biological prostheses\textsuperscript{23,25,50}. Since rest and exercise Doppler echocardiographic assessment of heart valve prostheses is subject to the same limitations, baseline data should be obtained before discharge from hospital after valve replacement to enable intra-individual comparison during follow-up.

An interesting application of stress echocardiography is assessment of the functional impact of valve replacement on left ventricular function. Wiseth et al.\textsuperscript{51} studied a group of patients with small aortic valve prostheses ($\leq$ 21 mm) detecting intraventricular flow towards the apex during isovolumic relaxation suggestive of left ventricular relaxation asynchrony in 24\% of the patients at rest and in 44\% during exercise. In 20\% of the patients an intraventricular gradient of 9 mmHg or greater was found at rest and in 40\% during exercise\textsuperscript{49}. These postoperative left ventricular functional abnormalities may be related to inadequate regression of left ventricular mass, stressing the fact that a prosthetic valve still represents an obstruction to outflow which in extreme cases leads to what has been coined by Rahimtoola as ‘valve prosthesis–patient mismatch’.

**Hypertrophic cardiomyopathy**

Doppler echocardiography permits accurate localization (subvalvular versus midventricular)\textsuperscript{52} and quantification\textsuperscript{50,53} of the obstruction in hypertrophic cardiomyopathy. The severity of the obstruction, which is dependent on contractility, peripheral resistance, and the size of left ventricular cavity, can vary substantially. Stress echocardiography is therefore an ideal tool for studying its dynamic character. Schwammenthal et al.\textsuperscript{54} and Decoulx et al.\textsuperscript{55} showed that the pressure gradient increases with exercise in most patients, although the response is not uniform\textsuperscript{53,56}. Millaire et al.\textsuperscript{56} pointed out that when all studies are taken together (Doppler as well as catheter) an increase in the pressure gradient is observed in 53\% of the patients, in 47\% no significant change or even a decrease can occur, although in patients with a significant resting gradient there is usually an increase (in 70\% of these patients). An important factor which will influence the increase of the pressure gradient (or lack of it) is body position during exercise, because the pressure gradient is higher in the upright position\textsuperscript{52}, while in the supine position augmented venous return with a subsequent rise of end-diastolic pressure may increase left ventricular size and thus limit or even prevent an increase in the pressure gradient during exercise\textsuperscript{57}. Remarkably, in almost all cases with significant resting obstruction, even when the gradient does not increase during exercise, a substantial increase is observed in the immediate post-exercise period, presumably because of an abrupt decrease in venous return, combined with a persistently low
peripheral resistance and continued sympathetic stimulation\textsuperscript{[5]}. Post-exercise assessment of the pressure gradient is therefore probably the most effective way of testing the dynamic character of the outflow tract obstruction.

Marwick et al. compared provocation of latent outflow tract obstruction by amyl nitrite and by exercise in 57 patients without significant resting obstruction\textsuperscript{[5]}, and distinguished certain features which were related to inducibility (small outflow tract dimensions, greater prevalence of 'septal bulge morphology', larger resting gradients). Interestingly, while in 26\% of the patients a significant gradient was provokable by both methods, in 11\% this could be achieved by exercise only, and in 18\% by amyl nitrite only.

While stress echocardiography may be useful for assessing the effect of medical or surgical therapy on the dynamic outflow tract obstruction (as well as in selecting patients suitable for subvalvular myectomy), it should be stressed that a relation between the pressure gradient (at rest or after provocation) and prognosis has not been demonstrated until now.

**Dilative cardiomyopathy**

The response of the myocardium to dobutamine infusion depends on the density and functional state of the \(\beta\)-receptors on the cell surface. In the failing heart, the depressed contractile function is paralleled by downregulation and uncoupling of these receptors (which may not necessarily represent the cause of reduced contractility, but rather a protective mechanism against cardiac catecholamine toxicity in the presence of elevated norepinephrine levels). Likewise, the improvement of left ventricular function following long-term \(\beta\)-blocker therapy is paralleled by normalization of the myocardial \(\beta\)-receptor pattern\textsuperscript{[6,7]}. Heilbrunn et al.\textsuperscript{[8]} demonstrated an improved haemodynamic response to dobutamine stimulation when assessing parameters of left ventricular systolic and diastolic function (LV dp/dt and end-diastolic pressure) following chronic \(\beta\)-blocker therapy. Again this was paralleled by an up-regulation of \(\beta\)-receptor density.

Assessing the prognostic implications of a reduced contractile reserve as well as testing the effect of medical therapy on the contractile response to dobutamine stimulation may become a clinically important goal of stress echocardiography in heart failure. In addition to conventional parameters of LV function (e.g. LV chamber volumes and ejection fraction) parameters of left ventricular shape or sphericity — indicative of increased wall stress, dysfunction and a poor prognosis — may be integrated into dobutamine or exercise studies. Tschler et al.\textsuperscript{[9]} have shown that, in contrast to conventional parameters of left ventricular function, a more spherical shape during peak exercise correlated strongly with a poor exercise function.

One particularly important application of assessing the contractile reserve by dobutamine stress testing may be monitoring cardiotoxic effects of chemotherapeutic agents. Dobutamine echocardiography has recently been shown to differentiate diminished myocardial function in asymptomatic doxorubicin-treated long-term survivors of childhood cancer\textsuperscript{[10]}. However, a prospective study is warranted to establish its value compared with alternative modalities of monitoring.

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